## REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-125 are in this case. Claims 12-14, 35-37, 54-56, 72-74, 89-91, 97 and 99-116 have been withdrawn from further consideration as being drawn to non-elected species. Claims 16-25 have been inadvertently withdrawn from further consideration as being drawn to non-elected species and should be examined on the merits (please see the remarks under the following "Election/Restriction" subsection). Claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125 have been rejected.

Claims 5, 6, 9, 11, 28, 29, 32, 34, 40, 41, 46-48, 51, 53, 60, 65, 66, 69, 71, 76-88, 92 and 120-123 have now been canceled. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 44, 45, 49, 50, 52, 57-59, 61-63, 67, 68, 70, 75, 93-95, 98, 117-119, 124 and 125 have now been amended. New claims 126-131 have been added.

### *Election/Restriction*

The Examiner has stated that Applicant's election of Perphenazine 4-aminobutyrate trihydrochloride in the reply filed on May 1, 2006 is acknowledged and has further stated that Applicant's indication of the claims that read on the species is accepted.

Applicant wishes to note in this respect, however, that in the reply filed on May 1, 2006, claims 16-25 were inadvertently omitted from the claims indicated as reading on the elected species. As the Examiner would have readily recognized, claim 16, pertaining to a pharmaceutical composition that comprises the conjugate of claim 1, is obviously a generic claim that reads on the elected species. Similarly, claims 17-25 read on the elected species and hence should be included within the claims that are currently being examined on the merits.

Applicant therefore respectfully requests that claims 16-25 will be included within the claims that are currently under examination. Accordingly, while Applicant has presently marked these claims as "Withdrawn" in the submitted amendment, Applicant has referred in the remarks below to amendments that should be introduced to these claims, based on the amendments made in corresponding claims in view of the Examiner's remarks.

The Examiner has further stated that claims 12-14, 16-25, 35-37, 54-56, 72-74, 89-91, 97 and 99-116 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected **invention**, there being no allowable generic or linking claim.

Applicant wishes to direct the Examiner attention in this respect to the Office Action mailed on March 30, 2006, in which the Examiner has stated that the Applicant is required to elect a single disclosed **species** and further that "***[u]pon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitation of an allowable generic claim as provided by 37 CFR 1.141***".

Applicant therefore believes that the Examiner's statement in the outstanding Office Action is erroneous and that claims 12-14, (16-25), 35-37, 54-56, 72-74, 89-91, 97 and 99-116 should be examined upon allowance of a generic claim. A new statement by the Examiner in this regard is therefore respectfully requested.

***Specification***

The Examiner has stated that the incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent or to a publication is improper and that Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection or other requirement imposed by the Office.

Applicant has thoroughly reviewed the specification of the instant application and has noted that the only non-patent publication that is incorporated by reference is: *"Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition*, cited on page 34, lines 10-12. Applicant asserts that this reference can be found in any scientific library and hence is within the public knowledge of any person skilled in the art. Applicant further asserts that while this reference was cited merely with respect to various routes for formulating drugs, this reference is not relied upon to overcome any objection, rejection or other requirement imposed by the Office and hence that no amendment should be made to the specification in this regard.

***35 U.S.C. § 112, first paragraph rejections***

The Examiner has rejected claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125, under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the species in the specification (AN-130, AN-167, AN-168, AN-177, AN-178, AN-180, AN-179, AN-181, AN-187 and AN-216), does not reasonably provide enablement for the compounds, compositions, method of use and process of preparing the compounds as claimed herein and does not enable any skilled in the art to which it pertains or for which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Claims 5, 6, 9, 11, 28, 29, 32, 34, 40, 41, 46-48, 51, 53, 60, 65, 66, 69, 71, 76-88, 92 and 120-123 have now been canceled. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 44, 45, 49, 50, 52, 57-59, 61-63, 67, 68, 70, 75, 93-95, 98, 117-119, 124 and 125 have now been amended. New claims 126-131 have been added.

More specifically, the Examiner has referred to the Wand factors and has stated that the claims of the instant application embrace compounds where a first chemical moiety is a psychotropic drug and a second chemical moiety is an organic acid residue of which the Applicant has neither supported nor contemplated. The Examiner has further stated that the specification of the instant application teaches about 9 examples where the psychotropic drug residue in the conjugate is the perphenazine core.

The Examiner has continued stating that the scope of "psychotropic disorder or disease", "neurodegenerative disorder or disease", "proliferative disorder or disease", "cancer" or "multidrug resistant cancer" cannot be deemed enabled and that the notion that a compound could be effective against these diseases and disorders in general is contrary to current understanding of how pharmacologicals work. The Examiner has further stated that prevention of these disorders is not remotely enabled.

The Examiner has stated that the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general predictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. The Examiner has noted that the test for determining compliance with 35 U.S.C. § 112 is whether the Applicant has clearly defined his invention.

The claims before the Examiner are directed to conjugates of psychotropic drugs and organic acids. As is discussed in the instant application (see, for example, the description starting on page 28 line 22 and ending on page 29 line 17), the psychotropic drugs and the organic acids are covalently linked to one another via a bond that is preferably cleavable within the body. Such bonds include, for example, ester bonds such as carboxylic ester bonds, thioester bonds and amide bonds. These conjugates are therefore designed so as to exhibit a therapeutic effect of each of the moieties comprising same.

In the Examples section of the instant application, the preparation of 10 exemplary conjugates has been demonstrated. These include conjugates of perphenazine and butyric acid (AN-167), 4-phenyl butyric acid (AN-130), propionic acid (AN-177), valeric acid (AN-178), and 4-aminobutyric acid (GABA) (AN-168); conjugates of fluphenazine and butyric acid (AN-180), propionic acid (AN-179), valeric acid (AN-181), and 4-aminobutyric acid (GABA) (AN-187); and a conjugate of valproic acid and GABA (AN-216). The synthetic pathway demonstrated for preparing these conjugates involves the simple, well-recognized nucleophilic addition reaction typically utilized for forming ester bonds between an organic acid and a hydroxy, amine, or thiol group or a carboxylic acid group of another chemical moiety.

In addition to these working examples, there is ample description in the specification of the instant application for routes of preparing the claimed conjugates. The Examiner's attention is directed in this respect, for example, to the description starting on page 19 line 18 and ending on page 33 line 11, where the preparation of conjugates of psychotropic drugs and organic acids, via hydroxy, thiol, amine or carboxylic acid group of the psychotropic drug and a carboxylic group of the organic acid is described in detail. It should be noted that all of the reactions described in the instant application are commonly used reactions that are widely described in the art and are well-known to any person skilled in the art.

In view of the above, it is respectfully argued that since the preparation of the conjugates described in the instant application is based on reacting a carboxylic acid group of an organic acid (the second moiety) with a suitable (e.g., amine, hydroxy or thiol) functional group of a psychotropic drug, to thereby form, via a simple nucleophilic-addition reaction, a corresponding ester bond between these groups, and further since such addition reactions of

carboxylic acid groups are simple, widely recognized and well-explored reactions, the specification of the instant application, by showing the feasibility to provide nine exemplary conjugates, provides a reasonable enablement for preparing the conjugates embraced by the instant application.

The Examiner's attention is also directed in this respect to MPEP 2164.02, where it is stated that the lack of working examples will not by itself render the invention non-enabled. Furthermore, MPEP 2164.02 states that for a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation.

Notwithstanding the above, and in order to expedite prosecution, Applicant has chosen to amend the claims so as to read on conjugates which comprise a residue of a psychotropic drug, whereas the psychotropic drug is phenothiazine that has a hydroxy, amine or thiol functional group covalently linked to an organic acid having 3-5 carbon atoms in its backbone.

Thus, claim 1 has been amended to recite:

"*[a] chemical conjugate comprising a first chemical moiety covalently linked to a second chemical moiety, wherein said first chemical moiety is a residue of a psychotropic drug, said psychotropic drug being a phenothiazine, said phenothiazine having a free amine, hydroxy, or thiol group before being conjugated to said second chemical moiety and further wherein said second chemical moiety is a residue of an organic acid, said organic acid having 3-5 carbon atoms in its backbone chain and further having a free carboxylic group before being conjugated to said first chemical moiety ....*"

Consequently, claims 6, 9 and 11, which included limitation now added to amended claim 1 or which included limitations that are no longer within the scope of claim 1, have been canceled. Similarly, claims , 29, 32, 34 and 40, 41, 46-48, 51, 53, 66, 69, 71 and 120-123 have been canceled.

Claims 2, 3, 8 and 10 have been amended so as to recite limitations that correspond to the scope and language of amended claim 1. Thus, claim 2 has been amended to no longer recite that the second moiety is an anti-proliferative residue, an analgesic residue or a GABA agonist residue and to recite instead that the second moiety is a γ-aminobutyric acid residue.

Claims 44, 62, and 94, have been similarly amended. Claim 3 has been amended to no longer recite the phrase "an alkoxy carboxylic ester bond". Claims 26, 45 and 63 have been similarly amended. Claim 8 has been amended to no longer recite the limitation "atypical psychotic drug residue". Claims 31, 50, and 68 have been similarly amended. Claim 10 has been amended to no longer recite psychotropic drugs other than phenothiazines. Claim 33, 52, 70 and 124 have been similarly amended. Claim 15 has been amended to recite those organic acids residues that were practiced in the preparation of the conjugates described in the working examples. Claims 38, 57, 75 and 125 have been similarly amended.

Applicant has further chosen to add new claim 126, which reads on a conjugate that comprises a perphenazine residue covalently linked to a γ-aminobutyric acid residue. Applicant has further chosen to add new claims 127-131, pertaining to a pharmaceutical composition, methods of treatment and methods of synthesizing, all utilizing a conjugate that comprises a perphenazine residue covalently linked to a γ-aminobutyric acid residue.

The Examiner's attention is directed in this respect to the working examples described herein, were the preparation of various conjugates comprising various combinations of two phenothiazines (perphenazine and fluphenazine) and five organic acids having 3-5 carbon atoms in their backbone (propionic acid, butyric acid, 4-phenyl butyric acid, 4-amino butyric acid and valeric acid) is described.

The Examiner's attention is further directed in this respect, for example, to page 22, lines 14-20, where it is recited that:

*"[p]articularly preferred psychotropic drugs, according to the present invention, are those having an amine group, a thiol group or an hydroxyl group, as these terms are defined hereinbelow, which can be reacted with the organic acid or a reactive derivative thereof. Such groups can be present in the psychotropic drug either as a free functional group or as a part of another functional group, e.g., an amide group, a carboxylic acid group and the like, as these terms are defined hereinbelow"*,

and to page 10, lines 1-3, where it is recited that:

*"[a]ccording to still further features in the described preferred embodiments the psychotropic drug residue is selected from the group consisting of a phenothiazine residue and a phenothiazine derivative residue".*

The Examiner's attention is further directed in this respect, for example, to page 24 lines 10-26, where it is recited that:

*"[t]he organic acid residue, according to the present invention, can be, for example, a residue that has a general formula -R-C(=O)-, where R can be, for example, a hydrocarbon residue that has 1-20 carbon atoms...*

*... the hydrocarbon residue according to the present invention can be alkyl or cycloalkyl....*

*... [m]ost preferably, the alkyl has 3 to 5 carbon atoms"*,

and to page 30 lines 17-20, where it is recited that:

" *... preferred organic acids according to the present invention include ... organic acids that have the general formula R-C(=O)-OH (corresponding to the organic acid residue R-(C=O)-O)*".

Applicant believes that the working examples, together with the description set forth from page 29, line 18 to page 33 line 33, are enabling with regard to making the claimed conjugates.

In response to the Examiner's remarks regarding how to use the invention, Applicant wishes to point out that the claims before the Examiner are directed to conjugates of psychotropic drugs and organic acids which exhibit reduced side effects as compared to the psychotropic drug when used *per se* and which further exhibit an anti-proliferative activity.

While, as is widely discussed in the instant application (see, for example, page 2, lines 17-23), treatment with psychotropic drugs such as phenothiazines is often associated with severe adverse side effects, the conjugation of an organic acid to the psychotropic drug was designed so as to reduce these side effects. As is further widely discussed in the instant application (see, for example, page 4, lines 15-30 and page 20, lines 9-11), the reduction of these side effects is attributed to the presence of GABA, which is known to affect the dopaminergic system that is involved in these adverse side effects. Similarly, such a reduction of the side effects can be effected by other organic acids that are structurally related to GABA, namely butyric acid, substituted butyric acid, propionic acid and valeric acid (see, for example, page 6, lines 21-22, and page 28, lines 2-5).

The conjugates described in the instant application were further designed so as to exhibit anti-proliferative activity. While, as is widely discussed in the instant application (see,

for example, the paragraph bridging pages 5 and 6 and page 6, lines 21-28), organic acids such as butyric acid and 4-phenyl butyric acids are well recognized anti-proliferative agents, whereby some psychotropic drugs, such as phenothiazines, are also known to exhibit such as activity. As is further widely discussed in the instant application, conjugating an organic acid that exhibits an anti-proliferative activity to a psychotropic drug results in improved anti-proliferative activity, especially in the brain, due to the affinity of the psychotropic derivative toward brain receptors and its improved brain pharmacokinetics (see, for example, the paragraph bridging pages 20 and 21).

The conjugates described in the instant application were further designed to exhibit chemosensitization activity, based on the chemosensitization effect exerted by some psychotropic drugs and the anti-proliferative activity of some organic acids (see, for example, the paragraph bridging pages 20 and 21).

In the working examples presented in the Examples section of the instant application, various conjugates of various combinations of two phenothiazines (perphenazine and fluphenazine) and five organic acids were tested for the effect of the conjugation on the side effects induced by the phenothiazines, for the anti-proliferative activity of the conjugates and for the chemosensitization activity of the conjugates. The obtained results clearly showed a multiple therapeutic effect of the tested conjugates, namely, reduction of the adverse side effects induced by the psychotropic drug while exhibiting an improved psychotropic activity (see, for example, Figures 1-11 and 22-28 and Tables 2 and 3) an anti-proliferative activity (see, for example, Figures 13-15 and Tables 4 and 5) and a chemosensitization activity (see, for example, Figures 16-18).

These data provide ample support for the underlying basis of the present invention, namely that conjugates of an organic acid and a psychotropic drug can be beneficially used in treating psychotropic diseases or disorder and further in treating proliferative disorders, either as anti-proliferative agents or as chemosensitizers.

These data, accompanied by the present knowledge of a person skilled in the art (as set forth, for example, in the Background section of the instant application) further provides a sufficient basis at least for predicting the effect of conjugating an organic acid to other psychotropic drugs, in terms of the effect of the organic acid on the GABA and the dopaminergic system, and hence for reducing dopamine-related side effects induced by the ]

psychotropic drug. These data further provides a sufficient basis at least for predicting the effect of conjugating an organic acid that has anti-proliferative activity to a psychotropic drug that has an anti-proliferative or chemosensitization activity, in terms of the enhanced activity and enhanced affinity to brain receptors.

Applicant wishes to direct the Examiner's attention again to MPEP 2164.02, where it is stated that the lack of working examples will not by itself render the invention non-enabled.

Notwithstanding the above, and in order to expedite prosecution, Applicant has chosen, as cited hereinabove, to amend the claims so as read on conjugates of a phenothiazine residue and an organic acid residue having 3-5 carbon atoms in its backbone chain.

As discussed in detail hereinabove, the data presented in the working examples of the instant application provides ample enablement for the effect of such conjugates in treating psychotic disorders that are known as treatable by phenothiazines. Particularly, these data clearly provides ample enablement for the efficacy of such conjugates in treating schizophrenia, a psychotic disorder that is widely known to be treatable by phenothiazines.

As further discussed in detail hereinabove, the data presented in the working examples of the instant application provides ample enablement for the effect of such conjugates in treating proliferative disorders, by showing the anti-proliferative effect of the conjugates on a variety of cancer cells.

As further discussed in detail hereinabove, the data presented in the working examples of the instant application provides ample enablement for the chemosensitizing effect of such conjugates, when used in combination with a variety of chemotherapeutic agents, in treating proliferative disorders.

Hence, while Applicant strongly believes that these data provide ample enablement for treating schizophrenia and related psychotic diseases, for treating cancer and other proliferative disorders and in chemosensitization, Applicant has chosen, in order to expedite prosecution, to further limit the scope of the claimed invention to the use of the conjugates in treating schizophrenia and cancer.

Thus, claim 39 has been amended to recite "*[a] method of treating schizophrenia ...*".

Consequently, claims 40 and 41, which included limitation that are no loner in the scope of amended claim 39, have been canceled.

Claim 58 has been amended to recite "*[a] method of treating cancer ...*".

Consequently, claim 60, which included the limitation now added to amended claim 58 has been canceled. Claim 59 has been amended to recite "cancer" instead of "proliferative disorder or disease". Claim 61, which previously depended from claim 60, has been amended so as to depend from claim 58.

Claims 76-88 and 92, which pertained to a method of chemosensitization, have now been canceled.

Applicant therefore believes to overcome the Examiner's rejection.

As detailed in response to the "Election/Restriction" item hereinabove, Applicant has also referred to claims 16-25 while responding to this rejection, although these claims are currently marked as withdrawn. Thus, claims 18, 19, 22 and 24, if subjected to examination, should be canceled. Claims 17, 20, 21, 23 and 25, if subjected to examination, should be amended as follows:

Claim 17 should be amended so as recite "schizophrenia" instead of "a psychotropic disorder or disease";

Claim 20 should be amended so as to recite "cancer" instead of "a proliferative disorder or disease";

Claim 21 should be amended to recite that "said cancer comprises ..." instead of "said proliferative disorder or disease is selected from the group consisting of";

Claim 23 should be amended to depend from claim 20 instead of claim 22; and

Claim 25 should be amended to recite that "... said second moiety is a γ-aminobutyric acid residue".

***35 U.S.C. § 112, second paragraph rejections***

The Examiner has rejected claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5, 6, 9, 11, 28, 29, 32, 34, 40, 41, 46-48, 51, 53, 60, 65, 66, 69, 71, 76-88, 92 and 120-123 have now been canceled. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 44, 45, 49, 50, 52, 57-59, 61-63, 67, 68, 70, 75, 93-95, 98, 117-119, 124 and 125 have now been amended.

Before referring to each of the Examiner's rejections in particular, Applicant wishes to collectively address the Examiner's rejections to phrases that include the term "residue".

The term residue is defined in the instant application, on page 21, lines 24-27, as follows:

"*...the term "chemical moiety" refers to* ***a residue*** *derived from a chemical compound, which retains its functionality...*

*[t]he term "residue" refers herein to a major portion of a molecule which is covalently linked to another molecule, as is well accepted in the art...*

Applicant asserts that the term "residue" as defined and used in the context of the instant application, clearly defines the moiety it describes and would be unambiguously interpreted by any person skilled in the art. The term "residue" is widely used in the art to describe the portion of an amino acid when present within a peptide. In peptides, two or more amino acids are covalently linked to one another via a covalent bond, formed upon a nucleophilic-addition reaction between a carboxylic end group of one amino acid and an amine end group of another amino acid residue. Upon such a reaction, a water molecule is typically released, whereby a major portion of each amino acid, which retains its functionality, is present in the obtained peptides. These major portions of amino acids are termed "residues" in order to distinct the structural features of an amino acid before and after the formation of a peptide containing same.

As argued hereinabove, the conjugates described in the instant application are similarly formed by reacting two functional groups of two substances, so as to form a bond therebetween. Taking together the widely recognized meaning of the term "residue" and the definition of this term as appears on page 21 lines 24 to 27, it is believed that any person skilled in the art would recognize that the term "residue" refers to that portion of a molecule that remains in a formed conjugate comprising same upon covalently linking a functional group thereof with another functional group of another moiety that forms the conjugate. It is therefore clear that the metes and bounds of claims that recite the term "residue" would be readily recognized by any person skilled in the art.

Notwithstanding the above, Applicant has chosen, in order to expedite prosecution, to amend independent claim 1 so as to more clearly define the claimed subject matter with respect to the term "residue". Thus, while, as delineated hereinabove, claim 1 has been

amended so recite conjugates of a phenothiazine that has a free amine, hydroxy or thiol group before being conjugated to the second chemical moiety and an organic acid that has 3-5 carbon atoms in its backbone chain a free carbocylic acid group before being conjugated to the first chemical moiety, claim 1 has been further amended to recite that:

*" .... whereas said residue of said phenothiazine is a portion of said phenothiazine that is formed upon reacting said amine, hydroxy or thiol group of said phenothiazine and said carboxylic group of said organic acid, and further whereas said residue of said organic acid is a portion of said organic acid that is formed upon reacting said carboxylic group with said amine, hydroxy or thiol group of said phenothiazines".*

Applicant believes that the term "residue" with respect to any of the chemical moieties cited in independent claim 1 and in claims that directly or indirectly depend therefrom is clearly defined and hence that the metes and bounds of claims that recite the term "residue" are set forth.

Referring now to each of the Examiner's rejection, in one particular, the Examiner has stated that claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125 are vague and indefinite in that it is not known what is meant by the "psychotropic drug residue", which does not set forth the metes and bounds of the claim.

Independent claim 1, as well as claims 2-11, 15-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125, have now been amended to no longer include the phrase "psychotropic drug residue", as delineated hereinabove in response to the 35 U.S.C. § 112, first paragraph rejection, and to recite instead, interchangeably, the phrases "a residue of a psychotropic drug" or simply "a psychotropic drug", whereas independent claim 1 has been further amended to recite that the psychotropic drug is a phenothiazine.

Applicant's remarks and amendments with respect to the term "residue" are delineated hereinabove.

Applicant asserts that the phrase "psychotropic drug" is widely known and used in the art to describe agents that exert their activity in the central nervous system. The Examiner's attention if directed in this respect to page 22, lines 1-4, of the instant application, where it is recited that "*... the phrase "psychotropic drug" encompasses any agent or drug that exerts an activity in the central nervous system and thereby can be used in the treatment of various central nervous system diseases or disorders*". Applicant therefore believes that any person

skilled in the art would readily recognize the meaning of the phrase "psychotropic drug" and hence that the this phrase clearly defines metes of bounds of the claims.

Applicant further asserts that the term "phenothiazine", which is widely known and used in the art to collectively describe tricyclic compounds having two end phenyl rings, each being fused to a thiazine ring, clearly defines the metes and bound of the claims.

Applicant therefore believes to have overcome the Examiner's rejection in this respect.

In another particular, the Examiner has stated that claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125 are vague and indefinite in that it is not known what is meant by the "organic acid residue", which does not set forth the metes and bounds of the claim.

Applicant believes that the phrase "organic acid residue" is well defined in the instant application. The Examiner's attention is directed in this regard to the definitions set forth on page 24, lines 4-13, which recite that:

*"[t]he phrase "organic acid residue" refers to a residue, as defined herein, that is derived from an organic acid that includes a free carboxylic group ...*

*[t]he term "free carboxylic group" includes a "-C(=O)OH" group either as is, in its protonated or in its ionized or salt state ....*

*... [t]he organic acid residue, according to the present invention, can be, for example, a residue that has a general formula R-C(=O)-, where R can be, for example, a hydrocarbon residue that has 1-20 carbon atoms*",

and further to page 30, lines 19-20, which recite:

*"... organic acids that have the general formula R-C(=O)-OH (corresponding to the organic acid residue R-(C=O)-O) ..."*

Applicant believes that the phrase "organic acid" has a clear meaning and is unambiguous interpreted by any person skilled in the art, and further strongly believes that the definitions and description set forth hereinabove even more clearly define both the phrase "organic acid" and the phrase "organic acid residue".

Applicant's additional remarks and amendments with respect to the term "residue" are delineated hereinabove.

Applicant therefore believes that the metes and bounds of amended independent claim 1 and of claims 2-11, 15-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125, which directly or indirectly depend therefrom, with respect to the term "organic acid residue" are clearly defined in the instant application.

Applicant therefore believes to have overcome the Examiner's rejection in this regard.

In still another particular, the Examiner has stated that claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125 are vague and indefinite in that it is not known what is meant by the "reduce side effects", which fails to set forth the degree or kind such that the questions of "which side effects" "reduced how much" and "where does it teach how to measure" may be answered.

Independent claim 1 has been amended in response to the 35 U.S.C. § 112, first paragraph rejection so as to more specifically define the claimed conjugate (see, Applicant's remarks hereinabove) and no longer recites the phrase "reduced side effects".

In still another particular, the Examiner has stated that claims 2, 44, 62, 79, 94, 117 and 119 are vague and indefinite in that it is not known what is meant by the "GABA agonist residue", which does not set forth the metes and bounds of the claim.

While Applicant believes that the phrase "GABA agonist residue" is well defined in the instant application, claims 2, 44, 62, 94, 117 and 119 have now been amended, in view of the amendments made in response to the 35 U.S.C. § 112, first paragraph rejection, to no longer recite this phrase, whereas claim 79 has been canceled. Amended claims 2, 44, 62, 94, 117 and 119 recite instead the phrase "γ-aminobutyric acid residue".

Applicant asserts that the phrase "γ-aminobutyric acid" describes a specific compound and is hence clearly defined. Applicant's remarks and amendments with respect to the term "residue" are delineated hereinabove.

Applicant therefore believes that the metes and bounds of the subject matter of claims 2, 44, 62, 94, 117 and 119 is clearly defined.

Applicant believes to have overcome the Examiner's rejection in this respect.

In still another particular, the Examiner has stated that claims 2, 44, 62, 79 and 94 are vague and indefinite in that it is not known what is meant by the "analgesic residue", which does not set forth the metes and bounds of the claim.

Since, as delineated hereinabove in response to the 35 U.S.C. § 112, first paragraph rejection, independent claim 1 has been amended so as to more specifically define the claimed conjugate, claims 2, 44, 62, 94, 117 and 119 have been accordingly amended to no longer include the phrase "analgesic residue", whereas claim 79 has been canceled.

In still another particular, the Examiner has stated that claims 2, 44, 62, 79 and 94 are vague and indefinite in that it is not known what is meant by the "anti-proliferative agent residue", which does not set forth the metes and bounds of the claim.

Since, as delineated hereinabove in response to the 35 U.S.C. § 112, first paragraph rejection, independent claim 1 has been amended so as to more specifically define the claimed conjugate, claims 2, 44, 62, 94, 117 and 119 have been accordingly amended to no longer include the phrase "anti-proliferative agent residue", whereas claim 79 has been canceled.

In still another particular, the Examiner has stated that claims 4, 27, 46, 64 and 81 are vague and indefinite in that it is not known what is meant by "anti-proliferative activity". The Examiner's rejection is respectfully traversed.

Applicant asserts that the phrase "anti-proliferative activity" is a widely recognized term, which is widely cited in publications, patents and patent applications worldwide. This term is self-explanatory as it is clear that any person skilled in the art would know the meaning of the phrase "anti-proliferative" and the meaning of the phrase "activity". In fact, searching the National Library of Medicine website "PubMed" (www.pubmed.gov) uncovered more than 500 scientific publications that cite this phrase.

In still another particular, the Examiner has stated that claims 5, 28, 47, 65 and 82 are vague and indefinite in that it is not known what is meant by "chemosensitization activity".

While Applicant believes that the term "chemosensitization" is well defined in the instant application (see, for example, page 23, lines 22-26), claims 5, 28, 47, 65 and 82, have been canceled upon limiting the claimed subject matter in response to the 35 U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove).

In still another particular, the Examiner has stated that claims 7, 30, 49, 67, 84 and 121 are vague and indefinite in that it is not known what is meant by the "anti-psychotic drug residue", which does not set forth the metes and bounds of the claim.

Applicant asserts that the phrase "anti-psychotic drug" is widely known and recognized term, used to describe a family of drugs that exert an anti-psychotic activity in the central nervous system. In fact, searching the USPTO Patents database uncovered 25 patents in which this phrase in recited in the claims and searching the National Library of Medicine website "PubMed" (www.pubmed.gov) uncovered more than 1,700 publications that cite this phrase.

Applicant's additional remarks and amendments with respect to the term "residue" are delineated hereinabove.

Applicant therefore believes that the phrase "anti-psychotic drug residue" is clearly defined and that the metes and bounds of claims 7, 30, 49, 67, 84 and 121 are set forth.

In still another particular, the Examiner has stated that claims 8, 31, 50, 68, 85 and 122 are vague and indefinite in that it is not known what is meant by the "typical anti-psychotic drug residue or atypical anti-psychotic drug residue", which does not set forth the metes and bounds of the claim.

Claims 85 and 122 have been canceled and claims 8, 31, 50 and 68 have been amended so as to more clearly define the scope of the claimed subject matter, in response to the 35 U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove). Claims 8, 31, 50 and 68 thus have been amended to no longer recite the phrase "atypical antipsychotic drug residue".

Nonetheless, Applicant asserts that the phrases "typical anti-psychotic drug" and "atypical anti-psychotic drug" are both widely known and recognized phrases, used to describe subfamilies of drugs that exert an anti-psychotic activity in the central nervous system. In fact, in most of the over 1,700 publications uncovered while searching the National Library of Medicine website "PubMed" (www.pubmed.gov), these phrases are cited. These phrases are also discussed and described in the instant application (see, for example, form page 2 line 6 to page 13 line 12).

Applicant's additional remarks and amendments with respect to the term "residue" are delineated hereinabove.

Applicant therefore believes that the phrases "typical anti-psychotic drug" is clearly defined and hence that the metes and bounds of claims 8, 31, 50 and 68 are set forth.

In still another particular, the Examiner has stated that claims 9, 32, 51, 69, 86 and 123 are vague and indefinite in that it is not known what is meant by "an anxiolytic drug residue, an anti-depressant residue, an anti-convulsive drug residue, an anti-parkinsonian drug residue, an acetylcholine esterase inhibitor residue, a MAO inhibitor residue, a tricyclic psychotropic drug residue, a bicyclic psychotropic drug residue, a monocyclic psychotropic drug residue, a phenothiazine residue, a benzodiazepine residue and a butyrophenone residue", which does not set forth the metes and bounds of the claim.

Claims 9, 32, 51, 69, 86 and 123 have now been canceled, in the amendments made in response to the 35 U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove).

In still another particular, the Examiner has stated that claims 10, 33, 52, 70, 87 and 124 are vague and indefinite in that it is not known what is meant by the agents' residues listed therein, which does not set forth the metes and bounds of the claim.

Claims 10, 33, 52, 70, 87 and 124 have been amended in response to the 35 U.S.C. § 112, first paragraph rejection, so as to recite that: "... *said psychotropic drug is selected from the group consisting of chlorpromazine, perphenazine, fluphenazine, and acetophenazine* ".

Since chlorpromazine, perphenazine, fluphenazine and acetophenazine are known compounds, Applicant believes that metes and bounds of claims 10, 33, 52, 70, 87 and 124 are set forth.

In still another particular, the Examiner has stated that claims 11, 34, 53, 71, 88 and 119 are vague and indefinite in that it is not known what is meant by the GABA agonists' residues listed therein, which does not set forth the metes and bounds of the claim.

Claims 11, 34, 53, 71, 88 and 119 have been canceled in Applicant's amendment in response to the 35 U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove.

In still another particular, the Examiner has stated that claims 15, 38, 57, 75, 92 and 125 are vague and indefinite in that it is not known what is meant by the organic acid residues listed therein, which does not set forth the metes and bounds of the claim.

Claims 15, 38, 57, 75, 92 and 125 have been amended in response to the 35 U.S.C. § 112, first paragraph rejection, so as to recite that: " ... *said organic acid residue is selected*

*from the group consisting of a butyric acid residue, a valeric acid residue, a 4-phenylbutyric acid residue, and an 4-aminobutyric acid residue*".

Applicant's remarks and amendments with respect to the term "residue" are delineated hereinabove.

Since butyric acid, valeric acid, 4-phenylbutyric acid, and 4-aminobutyric acid are known compounds, Applicant believes that metes and bounds of claims 15, 38, 57, 75, 92 and 125 are set forth.

In yet another particular, the Examiner has stated that claim 76 is vague and indefinite in that it is not known what is meant by "chemosensitization, in combination with a chemotherapeutic agent and/or in a medical condition for which chemosensitization is beneficial", which does not set forth the metes and bounds of the claim.

While, as argued hereinabove, Applicant believes that this phrase is well-defined in the instant application, claim 76 has been canceled in response to the 35 U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove).

In yet another particular, the Examiner has stated that claims 93-96, 98 and 117-125 are vague and indefinite in that it is not known what is meant by "psychotropic drug", which does not set forth the metes and bounds of the claim. Claims 95, 96, 98 and 120-123 have been canceled and claims 93, 94, 117, 119, 124 and 125 have been amended in response to the 35 U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove).

While Applicant believes that the phrase "psychotropic drug" is a well-known and widely recognize term, which is further clearly defined in the instant application, as delineated hereinabove, claims 93, 94, 117, 119, 124 and 125 have been amended in response to the 35 U.S.C. § 112 so as to no longer recite this phrase and to recite instead the term "phenothiazine".

Since, as argued hereinabove, the term "phenothiazine" is a well-known term used to describe compounds that have well-defined structural features, Applicant believes that the metes and bounds of claims 93, 94, 117-119, 124 and 125 are set forth.

In yet another particular, the Examiner has stated that claim 98 is vague and indefinite in that it is not known what is meant by "anti-proliferative agent", which does not set forth the metes and bounds of the claim. Claim 98 has now been amended, in response to the 35

U.S.C. § 112, first paragraph rejection (see, Applicant's remarks hereinabove), so as to no longer include the phrase "anti-proliferative agent".

In yet another particular, the Examiner has stated that claims 95 and 98 are vague and indefinite in that it is not known what is meant by "acyl chloride derivative", which implies more then what is positively recited.

Applicant wishes to point out that the phrase "acyl chloride" describes a well-defined chemical group and further that the phrase "acyl chloride derivative" in cited in claims 95 and 98 with respect to an organic acid. Since the term "acyl" clearly indicates that the acyl chloride group is derived from a carboxylic group and further since it is well recognized and is further recited in particular in claim 1, from which claims 95 and 98 depend, that the organic acid has a free carboxylic group, Applicant believes that any person skilled in the art would acknowledge the exact meaning of this phrase. However, in order to expedite prosecution and to more clearly define the claims subject matter, Applicant has chosen to amend claims 95 and 98 so as to recite:

" ... *converting said free carboxylic group in said organic acid into an acyl chloride group*".

Applicant believes that the subject matter of amended claims 95 and 98 is now clearly defined in this regard.

In yet another particular, the Examiner has stated that claim 98 is vague and indefinite in that it is not known what is meant by "thiol derivative", which implies more then what is positively recited.

Claim 98 has now been amended so as to recite "... *converting an amine or hydroxyl group of said phenothiazines to a thiol group ...*".

Applicant believes that the subject matter of amended claim 98 is now clearly defined in this regard.

In yet another particular, the Examiner has stated that claim 118 is vague and indefinite in that it is not known what is meant by "acyl imidazole derivative", which implies more then what is positively recited.

Applicant wishes to point out that the phrase "acyl imidazole" describes a well-defined chemical group and further that the phrase "acyl imidazole derivative" in cited in claim 118 with respect to an organic acid. Since the term "acyl" clearly indicates that the

acyl imidazole group is derived from a carboxylic group and further since it is well recognized and is further recited in particular in claim 1, from which claim 118 depends, that organic acids has a free carboxylic group, Applicant believes that any person skilled in the art would acknowledge the exact meaning of this phrase. However, in order to expedite prosecution and to more clearly define the claims subject matter, Applicant has chosen to amend claim 118 so as to recite:

" ... *converting said free carboxylic group in said organic acid into an acyl imidazole group*".

Applicant believes that the subject matter of amended claim 188 is now clearly defined.

Applicant therefore believes to have overcome the Examiner's rejections.

As detailed in response to the "Election/Restriction" item hereinabove, Applicant has also referred to claims 16-25 while responding to these rejections, although these claims are currently marked as "Withdrawn".

Thus, being dependent from claim 1, and in view the amendments cited hereinabove with respect to these claims in response to the 35 U.S.C. § 112, first paragraph rejection, and further in view of the amendments and remarks delineated hereinabove, Applicant believes that the metes and bounds of these claims are set forth.

***35 U.S.C. § 102(e) rejection***

The Examiner has rejected claims 1-11, 15, 26-34, 38-53, 57-71, 75-88, 92-96, 98 and 117-125, under 35 U.S.C. § 102(e) as being anticipated by Borisy et al, U.S. Patent No. 6,569,853. The Examiner's rejection is respectfully traversed. Claims 5, 6, 9, 11, 28, 29, 32, 34, 40, 41, 46-48, 51, 53, 60, 65, 66, 69, 71, 76-88, 92 and 120-123 have now been canceled. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 44, 45, 49, 50, 52, 57-59, 61-63, 67, 68, 70, 75, 93-95, 98, 117-119, 124 and 125 have now been amended.

Specifically, the Examiner has stated that Borisy et al. teach the elements such as perphenazine, where the perphenazine ring is substituted by $-C(O)CH_3$ or $-C(O)-(CH_2)_5-CH_3$, and that the compounds are for the same uses as claimed in the instant application.

Applicant wishes to point out that Borisy et al. teach **phenothiazines** that are substituted by a variety of substances at a variety of positions. Applicant wishes to further

point out that, as is well known in the art, phenothiazines is a collective term used to describe tricyclic compounds that have two end phenyl groups that are each fused to a thiazine ring, whereas perphenazines belong to a subfamily of phenothiazines, which possess a piperazine side chain at the thiazine ring.

Notwithstanding the above, Borisy et al. teach, amongst the various compounds describes therein, two compounds in which a phenothiazine is substituted by a carboxylic ester moiety (see, Formulae B-3 and B-12). While these compounds can be referred to conjugates of a phenothiazine and an organic acid, linked via a carboxylic ester bond, these conjugates include a residue of an organic acid that is derived from acetic acid (for Formula B-3) and from heptanoic acid (for Formula B-12) and hence derived from organic acids that have 2 and 7 carbon atoms in the chain thereof, respectively.

Claim 1 has now been amended so as to recite that the organic acid residue in the claimed conjugate has 3-5 carbon atoms in its backbone chain.

Since Borisy et al. teaches conjugates of a phenothiazine and an organic acid that has 2 or 7 carbon atoms in its chain, Borisy et al. fail to teach the claimed conjugates.

Moreover, Borisy et al. teach an anti-proliferative combination of a chlorpromazine, or analogs and derivatives thereof and the antiprotozoal drug phentamidine. Thus, Borisy et al. teaches that the various phenothiazines taught therein, which are analogs and derivatives of chlorpromazine, are useful in the treatment of cancer and other neoplasms when administered in combination with phentamidine, simultaneously or within 14 days of each other.

Borisy et al. therefore fail to teach a method of treating cancer, which is effected by administering a conjugate of a phenothiazine and an organic acid as the sole active ingredient. Borisy et al. further fail to teach or remotely suggest the use of the substituted phenothiazines taught therein in treating psychotropic disorders.

In sharp distinction, as argued hereinabove, the present invention teaches conjugates of phenothiazines and organic acids, which were designed so as to exhibit both anti-psychotic activity and anti-proliferative activity. More particularly, these conjugates were designed such that the coupling of the phenothiazines to an organic acid would result in reduction of the side effects known to be involved with administration of phenothiazines and/or such that the resulting conjugate would exhibit an anti-proliferative activity.

As is demonstrated in the Examples section of the instant application, various conjugates of phenothiazines and organic acids having 3-5 carbon atoms in a chain thereof have been tested and were found highly active in inhibiting proliferation of various types of cancer cells, when utilized as the sole active ingredient. These conjugates were further found to exhibit an anti-psychotic activity in a well-known model for Schizophrenia and were further found to exhibit reduced side effects as compared to the corresponding phenothiazines when utilized *per se*.

It is therefore clear that since (i) Borisy et al. fail to teach conjugates of a phenothiazine and an organic acid that has 3-5 carbon atoms in its chain; (ii) Borisy et al. fail to teach the use of these and other conjugates of phenothiazines and organic acids, as the sole active ingredient, in treating cancer; and (iii) Borisy et al. fail to teach the use of these and other conjugates of phenothiazines and organic acids in treating schizophrenia and other psychotic and psychotropic diseases and disorder, Borisy et al fails to teach or remotely suggest the claimed conjugates and their use in treating schizophrenia cancer and related diseases or disorders.

It is further clear that since the compounds taught in Borisy et al. are merely derivatives and analogs of chlorpromazine, which are aimed to be used in combination with phentaminide in treating cancer, Borisy et al. are completely silent with respect to the effect of conjugating organic acids to phenothiazines in order to reduce the phenothiazine's side effect or to exhibit an anti-proliferative activity. Borisy et al. therefore provide no motivation to design and practice the conjugates taught by the present invention.

It is therefore the Applicant's opinion that claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-44, 45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124 and 125 are not anticipated by Borisy et al. and are therefore allowable.

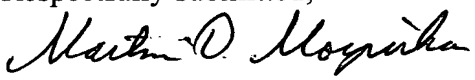
***Examination of Generic and Non-Elected Claims***

In view of the amendments made to the claims and the arguments recited herein it is believed that the claims are allowable with respect to the elected species and hence examination of claims 1-4, 7, 8, 10, 12-14, 15-27, 30, 31, 33, 35-39, 42-44, 45, 49, 50, 52, 54-59, 61-64, 67, 68, 70, 72-75, 93-119, 124 and 125 in their generic context and with respect to all the species recited therein is respectfully requested. Applicant wishes to point out that

upon examination of the claims in generic context, Applicant is willing to introduce the amendments submitted herein to claims currently withdrawn from examination.

In view of the above amendments and remarks it is respectfully submitted that amended claims 1-3, claim 4, amended claims 7, 8, 10, 15, 26, claim 27, amended claims 30, 31, 33, 38 and 39, claims 42 and 43, amended claims 44, 45, 49, 50, 52, 57-59 and 61-63, claim 64, amended claims 67, 68, 70, 75, 93-95, claim 96, amended claims 98, 117-119, 124 and 125 and new claims 126-131 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,



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Date: November 15, 2006

***Encl.:***
Petition for Extension for one (1) month time